

Manual for Expedited Reporting of Adverse Events to DAIDS

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1.0 PURPOSE OF MANUAL

1.1 Purpose

The purpose of this Manual is to describe the criteria and method for expedited reporting of certain serious and other reportable adverse events to the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), through the DAIDS Safety Office.

1.2 Scope

This Manual applies only to those clinical studies/trials requiring expedited reporting of adverse events to the DAIDS Safety Office as stated in the protocol.

This Manual applies to all study agents specified in the protocol as requiring expedited reporting to DAIDS. Although not covered under this Manual, note that DAIDS may require MedWatch reporting (using e.g., Form FDA 3500A or CIOMS I Form) to the Food and Drug Administration (FDA) and/or DAIDS for some studies. MedWatch reporting may only be applied to studies/trials of US FDA-approved study agents. Any requirements for MedWatch reporting will be identified in the study/trial protocol.

1.3 Introduction

For adverse events requiring expedited reporting to DAIDS, sites must follow the general reporting requirements and procedures described in this Manual. In order to fully define the expedited adverse event reporting requirements that apply to an individual study/trial, the protocol will specify:

- One of three Levels of Adverse Event Reporting (Section 3.1) and any other adverse events to be reported on an expedited basis (Section 3.2).
- The duration of the protocol-defined expedited reporting period.
- The name or category of each study agent (US FDA-approved or investigational) that requires expedited reporting of adverse events to DAIDS. This may include study agents in addition to those provided by the study/trial.

2.0 DESCRIBING AN ADVERSE EVENT BY SERIOUSNESS, SEVERITY, RELATIONSHIP TO STUDY AGENT, AND EXPECTEDNESS

The criteria for expedited reporting of adverse events to the DAIDS Safety Office include the seriousness of the outcome of the event, the severity (intensity) of the event, its relationship to study agent, and (only for the Targeted Level) expectedness, i.e., whether the adverse event is expected or unexpected.

2.1 Seriousness

The first consideration for expedited reporting of adverse events to DAIDS is the seriousness of the outcome of the event. The April 1996 International Conference on Harmonisation (ICH) guidance, “Good Clinical Practice: Consolidated Guidance,” (ICH E6) defined a serious adverse event (SAE) as “any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.”

“Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above” may also be considered to be serious. (October 1994 ICH guidance (E2A), “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.”)

2.2 Severity (Intensity)

The second consideration for expedited reporting of adverse events to DAIDS is the severity (intensity) of the event. In order to maintain consistency among studies/trials and sites, DAIDS has developed a list of common clinical and laboratory adverse events and defined grade 1 – 5 severity parameters to generate the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (also known as “the toxicity tables”). These tables are located on the DAIDS Safety Office website at <http://rcc.tech-res-intl.com>.

Unless stated otherwise in the protocol, study staff is required to use the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences to determine the intensity of adverse events in order to establish consistency in adverse event reporting to DAIDS. Specific protocols may include additional or modified criteria for grading adverse events that are not included in the current versions of the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences.

2.3 Seriousness vs. Severity (Intensity) of Adverse Events and Reporting Criteria

For expedited reporting to DAIDS, the term “severity” (or “intensity”) is described as the grade for a specific event, i.e., mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). This is *not* the same as “serious,” which is based on subject/event *outcome or action* criteria usually associated with events that pose a threat to a subject’s life or functioning (ICH E2A).

2.4 Relationship to Study Agent

The third consideration for expedited reporting of adverse events to DAIDS is the judgment of causal association (relationship) between an adverse event and the study agent. The protocol must specify by name or category each study agent (either approved or investigational) that requires expedited reporting of adverse events to DAIDS. The study physician makes the site’s final assessment of the causal association based upon the temporal relationship to administration of the study agent(s), the pharmacology of the study agent(s), and his/her clinical judgment.

The terms used in DAIDS studies/trials to assess relationship of an event to study agent are:

- **Definitely Related.** The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
- **Possibly Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.
- **Probably Not Related.** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.
- **Not Related.** The adverse event is clearly explained by another cause not related to the study agent.
- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to study agent are being collected. The site is required to submit a final assessment within 3 business days after reporting the death. If no final assessment is made within 3 business days after the date of submission, the event will be assessed as possibly related to study agent. Any additional information received at a later time, including an autopsy report, should be submitted as a Follow-up Report.

A **suspected adverse drug reaction (SADR)** is an adverse event that could potentially have a causal relationship to the study agent (definitely, probably, possibly, probably not related, or for deaths, pending).

2.5 Expectedness (Expected vs. Unexpected)

Expected refers to the perspective of events previously observed, *not* on the basis of what might be anticipated from the pharmacological properties of the study agent. (ICH E2A)

Unexpected refers to events whose nature or severity (intensity) is not consistent with those included in the package insert/summary of study agents that have been approved by the US FDA or in the Investigator's Brochure. (ICH E2A)

3.0 ADVERSE EVENTS REQUIRING EXPEDITED REPORTING AND THE STUDY/TRIAL REPORTING PERIOD

3.1 Levels of Adverse Event Reporting

The protocol will specify one of three Levels of Adverse Event Reporting. The Level of Adverse Event Reporting chosen for expedited reporting is based primarily upon the degree of risk that may be associated with the study agent.

3.1.1 Standard Level

Report all adverse events following any exposure to study agent that:

- Result in death **regardless** of relationship to study agent.
- Are congenital anomalies, birth defects, or fetal losses **regardless** of relationship to study agent.
- Result in persistent or significant disabilities or incapacities **regardless** of relationship to study agent.
- Are a **suspected adverse drug reaction**, i.e., definitely, probably, possibly, and probably not related, to a study agent that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death.
- Are life-threatening (including all Grade 4 adverse events) **suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent.

3.1.2 Intensive Level

In addition to all adverse events reported for the Standard Level, also report all Grade 3 suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent. (The Intensive Level includes reporting Grades 3 and 4 SADR.)

3.1.3 Targeted Level

Use of the Targeted Level of reporting is limited to non-IND studies/trials of US FDA-approved agents and doses for approved indications and populations. Report **only** the following adverse events:

- All events that result in death **regardless of relationship** to study agent.
- All congenital anomalies, birth defects, or fetal losses **regardless of relationship** to study agent.
- All persistent or significant disability or incapacity **regardless of relationship** to study agent.
- **Unexpected* suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent, that require or prolong existing hospitalization, or require intervention to prevent death or significant/permanent disability.
- **Unexpected* life-threatening clinical suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent. **DO NOT report** Grade 4 laboratory values that are not associated with a life-threatening clinical event.

*Unexpected events are events whose nature or severity is not consistent with the package insert/summary of product characteristics for a US FDA-approved study agent.

3.2 Additional Protocol-Required Expedited Reporting Requirements

In addition to specifying one of the reporting levels above, a protocol may require other adverse events to be reported on an expedited basis. In this case, the protocol will explicitly state the additional adverse events to be reported to DAIDS. For example, in rare instances a protocol may specify use of the Intensive Level and also require Grades 1 and 2 SADRs to be reported, or a protocol may require reporting of a specific type of adverse event regardless of grade.

3.3 Additional Adverse Events That Should Be Reported for Any Study/Trial Requiring Expedited Reporting to DAIDS

In addition to the reporting requirements described above, sites should report any of the following adverse events on an expedited basis:

- Suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that **do not meet the protocol-required reporting criteria**, but the Investigator believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes adverse events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent a serious adverse event. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions that do not result in hospitalization.

- Unexpected, serious suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that occur at any time **after the protocol-defined expedited reporting period** if the study staff become aware of its occurrence. These events include deaths, permanent disabilities, congenital anomalies, hospitalizations, and life-threatening clinical events. (Do not report Grade 4 laboratory values unless associated with a life-threatening clinical event.)
- Serious adverse events that are not related to a study agent, but could be associated with **study participation or procedure** (e.g., pulmonary embolism secondary to an intravenous catheter placed for study agent administration).

3.4 Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject, and if so, the protocol must specify the duration of this additional reporting period.

4.0 METHOD AND TIMEFRAME FOR EXPEDITED REPORTING OF INDIVIDUAL ADVERSE EVENTS

All information requested on the DAIDS Expedited Adverse Event Reporting Form must be provided and the form submitted to the DAIDS Safety Office. This form can be found at the web site for the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided in Appendix B.

The timeframe for expedited reporting of individual adverse events begins when the site recognizes that an event fulfills the criteria outlined in this Manual for expedited reporting to DAIDS. Sites must submit adverse events requiring expedited reporting to the DAIDS Safety Office as soon as possible, **but no later than 3 business days**, after the site's recognition that the event fulfills the criteria for expedited reporting.

5.0 ADDITIONAL EXPEDITED REPORTING REQUIREMENTS

5.1 Follow-up Reporting of Adverse Events

5.1.1 Submitting Follow-Up Information on Adverse Events

For the circumstances listed below, the site is required to submit follow-up information when it becomes available on a new Expedited Adverse Event Form as a Follow-up Report.

- Requests by DAIDS for additional information.
- A change in the relationship between the adverse event and study agent by the study physician.
- Additional significant information that becomes available for a previously reported adverse event. This is particularly important for new information addressing cause of death if the initial assignment was “pending.”
- Results of rechallenge with the study agent(s), if performed.

5.1.2 Outcome of Adverse Events

The site **must** follow each reported adverse event and record eventual outcomes in the source documentation. However, report of the outcome of a reported adverse event to the DAIDS Safety Office is not required unless specifically requested by DAIDS.

5.2 Reporting Recurrent Adverse Events

For events that have been previously reported to the DAIDS Safety Office, if the event has fully resolved and then re-occurs to a level requiring expedited reporting, the adverse event must be reported as a New Report to the DAIDS Safety Office.

5.3 Reporting Change in Severity of Adverse Events

Any ongoing event that increases in severity to a higher grade than previously reported must be reported again as a New Report on a new DAIDS Expedited Adverse Event Reporting Form.

Ongoing events that improve, but are not resolved, and then increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office. Resolution is the normalization or return to baseline (i.e., prior to study agent exposure) of laboratory values, signs, or symptoms related to the event.

5.4 Study Physician Assessment and Signature

A study physician listed on the Form FDA 1572 for IND studies or the DAIDS Investigator of Record Agreement (IoR) for non-IND studies must review and verify the data on the DAIDS Expedited Adverse Event Reporting Form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study agent and the adverse event. This physician must sign the completed DAIDS Expedited Adverse Event Reporting Form. If necessary to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 business days.

6.0 APPENDICES

6.1 Appendix A: Definition of Terms

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a casual relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6) (Synonym: Adverse Experience)

DAIDS Safety Office: The Office to which adverse events requiring expedited reporting are submitted. (DAIDS)

Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (Toxicity Tables): Lists of common terms and severity (intensity) parameters used to describe adverse events occurring in DAIDS-sponsored clinical studies/trials. (DAIDS)

IND: An investigational new drug application. (21 CFR 312.3)

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. (ICH E6)

Non-IND Study/Trial: A study/trial for which there is no IND filed with the US FDA.

Package Insert: The approved package circular in marketed drug packaging containing the drug description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, dosage and administration, how drug is supplied, "clinical studies," and "references." (21 CFR 201.57)

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E6 and E2A)

Study Agent: Drugs, biological products, or combination of drugs and biological products (approved or investigational) defined in the protocol as requiring expedited reporting to DAIDS. (DAIDS)

Study Physician: A physician listed on the Form FDA 1572 for IND studies or on the DAIDS Investigator of Record Agreement (IOR) for non-IND studies. (DAIDS)

Suspected Adverse Drug Reaction (SADR): An adverse event that could potentially have a causal relationship to a study agent (definitely, probably, possibly, probably not related or for deaths, pending). (DAIDS)

Toxicity: An adverse event that has an attribution of possibly, probably, or definitely related to a study agent. (DAIDS) NOTE: This term should not be used for expedited reporting of adverse events to DAIDS.

Unexpected Event: An adverse event, the nature or severity (intensity) of which is not consistent with the applicable product information (Investigator's Brochure, package insert, or summary of product characteristics for a US FDA-approved study agent. (DAIDS)

6.2 Appendix B: Contact Information for DAIDS Safety Office

All completed DAIDS Expedited Adverse Event Forms are submitted to the DAIDS Safety Office.

For questions or other communication, please note the following:

Website:	http://rcc.tech-res-intl.com
Office Phone*:	1-800-537-9979 (US only) or +1-301-897-1709
Office Fax*:	1-800-275-7619 (US only) or +1-301-897-1710
Office Email:	RCCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM (US Eastern Time)
Mailing Address:	DAIDS Safety Office 6500 Rock Spring Drive Suite 650 Bethesda, MD 20817

*Office phone and fax are accessible 24 hours per day.

6.3 Appendix C: Summary Chart for Expedited Reporting of Adverse Events to DAIDS for Protocol-Specified Study Agents

	Standard Level	Intensive Level	Targeted Level
Deaths	All Events	All Events	All Events
Congenital anomalies, birth defects, fetal losses	All Events	All Events	All Events
Disabilities/Incapacities	All Events	All Events	All Events
Hospitalization¹	All Suspected Adverse Drug Reactions ²	All Suspected Adverse Drug Reactions ²	Unexpected Suspected Adverse Drug Reactions ^{2,3}
Other events	All Grade 4 Suspected Adverse Drug Reactions ²	All Grades 3 and 4 Suspected Adverse Drug Reactions ²	Unexpected Life-Threatening Clinical Suspected Adverse Drug Reactions ^{2,3}

¹This category includes hospitalization, prolongation of hospitalization or requirement of intervention to prevent permanent disabilities or death.

²Suspected adverse drug reactions are adverse events that are assessed as definitely, probably, possibly, probably not related to a study agent (or for deaths, pending).

³Unexpected events are adverse events, of a nature or severity (intensity) that is not consistent with the applicable product information (package insert/summary of product characteristics) for a US FDA-approved study agent.

Timeframe for Expedited Reporting of Individual Adverse Events:

Adverse events requiring expedited reporting are to be reported to the DAIDS Safety Office **no later than 3 business days** after the site's recognition that the event fulfills the criteria for expedited reporting.

Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject.